Lung adenocarcinoma promotion by air pollutants

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Abstract

A complete understanding of how exposure to environmental substances promotes cancer formation is lacking. More than 70 years ago, tumorigenesis was proposed to occur in a two-step process: an initiating step that induces mutations in healthy cells, followed by a promoter step that triggers cancer development^ 1 . Here we propose that environmental particulate matter measuring ≤2.5 μm (PM_2.5), known to be associated with lung cancer risk, promotes lung cancer by acting on cells that harbour pre-existing oncogenic mutations in healthy lung tissue. Focusing on EGFR-driven lung cancer, which is more common in never-smokers or light smokers, we found a significant association between PM_2.5 levels and the incidence of lung cancer for 32,957 EGFR-driven lung cancer cases in four within-country cohorts. Functional mouse models revealed that air pollutants cause an influx of macrophages into the lung and release of interleukin-1β. This process results in a progenitor-like cell state within EGFR mutant lung alveolar type II epithelial cells that fuels tumorigenesis. Ultradeep mutational profiling of histologically normal lung tissue from 295 individuals across 3 clinical cohorts revealed oncogenic EGFR and KRAS driver mutations in 18% and 53% of healthy tissue samples, respectively. These findings collectively support a tumour-promoting role for PM_2.5 air pollutants and provide impetus for public health policy initiatives to address air pollution to reduce disease burden. Combination of epidemiology, preclinical models and ultradeep DNA profiling of clinical cohorts unpicks the inflammatory mechanism by which air pollution promotes lung cancer